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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|-----------------|-------------|----------------------|---------------------|------------------|
| 09/411,863 | 10/04/1999 | SHAMAY IZHAR | 1620/3 | 8900 |

7590 02/08/2002
SOL SHEINBEIN
G.E. EHRLICH (1995) LTD. c/o ANTHONY CASTORINA
2001 JEFFERSON DAVIS HIGHWAY
SUITE 207
ARLINGTON, VA 22202

EXAMINER

KUBELIK, ANNE R

ART UNIT PAPER NUMBER

1638

DATE MAILED: 02/08/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/411,863

Applicant(s)

IZHAR, SHAMAY

Examiner

Anne Kubelik

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-9 and 11-57 is/are pending in the application.
- 4a) Of the above claim(s) 1-9, 11-46, 48 and 52-54 is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☒ Claim(s) 47, 49-51 and 55-57 is/are rejected.
- 7) ☐ Claim(s) ____ is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on ____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. ____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). ____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) ____ 6) ☐ Other: ____

DETAILED ACTION

1. As requested in Paper No. 11, filed 15 November, 2001, claims 47, 49-51 and 55 have been amended. Claims 1-9 and 11-57 are pending. Claims 1-9, 11-46, 48, and 52-54 are withdrawn from consideration as being drawn to nonelected inventions. Claims 47, 49-51 and 55-57 are examined.
2. In all claims that were amended for the second time --Twice-- was inserted before "Amended". Applicant is reminded that if the claims are amended a third time, they need to say "Thrice amended".
3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Response to Argument

4. The rejection of claim 51 under 35 U.S.C. 103(a) as being unpatentable over Lloyd et al in view of Snaith et al is WITHDRAWN as the plasmids of Snaith et al would not produce expression cassettes in which the first segment is flanked by SSRS's and the second segment is flanked by different SSRS's, but only ones in which each segment is flanked by different SSRS's.

Claim Objections

5. Claims 47 and 49 are objected to because of the following informalities: There is a disagreement between the use of "plants" and the use of "a" in claim 47's recitation of "a first and a second plants" in past (a); it is suggested that the phrase be replaced with --a first plant

and a second plant--. Additionally, either an --a-- is needed before “progeny in part (c) of claim 47 and parts (b) and (c) of claim 49 or “is” should be replaced with --are-- in all these steps. Lastly, “resultant in claim 47, parts (c) and (d), and claim 49, part (d), “resultant” should be replaced with --resulting--. Appropriate correction is required.

Claim Rejections - 35 USC § 112

6. Claims 47, 49 and 56-57 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, as stated in the prior Office action.

Applicant’s arguments filed 15 November, 2001, have been fully considered but they are not persuasive.

Applicant urges that the recombination steps described by Qin et al and Golic would not exist in any plants or any steps used by the invention. Applicant urges that the recombinase gene is selected out in the following generation of the progeny of the recombination event, and that the claims 47 and 49 have now been amended to reflect this step. Applicant also urges that interchromosomal events are not possible because the plant subjected to recombination can be a heterozygous plant. Applicant also argues that methods of generating these plants need not do so with 100% efficiency. Applicant argues that the prior art methods employ recombinases to reverse an established phenotype, while the present invention generates plants in which exogenic allelism is reversed by plant breeding techniques, thereby eliminating uncontrolled excision/recombination. In response to Lloyd et al, cited in the prior Office action, Applicant

points out that Lloyd et al find it interesting that FLP/FRT recombination failed in *Arabidopsis* and could provide no explanation for it. Additionally, Applicant points out that others, including Kilby et al, have used FLP/FRT successfully in *Arabidopsis*. Lastly, Applicant urges that although Luo et al report an improved FLP/FRT construct for use in *Arabidopsis*, their results do not imply that the widely used system would not function in any plant.

This is not found persuasive. Gidoni et al (2001, *Euphytica* 121:145-156) teach that while germinal transmission of the recombined loci is a pre-requisite for a variety of applications of site-specific recombination in plants, including that of the instant application (pg 155, left column, paragraph 2), substantial variation occurs in the timing of FLP recombinase activity (pg 146, left column, paragraph 2). Gidoni et al also teach the necessity of selecting hybrids that show early FLP activity and of selecting both FLP and target FRT lines that facilitate early recombination (pg 154, left column, paragraph 2). Additionally, Gidoni et al teach that identifying crosses that activate recombination in seeds, rather than later in development, is required because no or inefficient germinal inheritance results from these late recombination events, as measured by construct inheritance in F2 progeny (pg 154, right column, paragraphs 2-3). Lastly, the only line in which Gidoni et al got germinal inheritance used the constructs of Luo et al (Gidoni et al, pg 146, left column, paragraph 3, and pg 154, right column, paragraph 3), supporting arguments made in the prior Office actions. As the instant invention requires the use of properly recombined F2 progeny, and as the instant specification fails to teach the need for establishing germinal inheritance and the modification of Luo et al, undue experimentation would be required to analyze a multitude of progeny to find the one that have the exogenes in the desired allelic relationship.

While step (c) of claim 47 selects out the recombinase gene in following generation of the progeny of the recombination event, nothing is done with these resulting recombinase minus plants, as the step (d) uses the plant from step (b) in the cross. Thus, problems associated with the continued presence of the recombinase remain.

Lastly, the claims are drawn to a method step of introducing a recombinase into a plant. The instant specification fails to provide guidance for topical application of a recombinase protein to a plant, for getting the applied protein into the plant, and for having it reliably result in specific recombination. The instant specification only provides guidance for introduction inot a plant of a nucleic acid encoding a recombinase. In the response filed 15 November, 2001, Applicant did not provide an explanation for how topical application of the recombinase is enabled by the specification.

7. Claims 50-51 and 55 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant's arguments filed 15 November, 2001, have been fully considered but they are not persuasive.

Applicant urges that the plants are characterized by exogenic allelism and are thus readily distinguishable from other nontransformed plants, and that the plants could readily be typed by PCR or Northern blotting.

This is not found persuasive. The instant specification fails to describe the sequence of the promoters, transcribable polynucleotide sequences, and recombination sequences in these plants and fails to describe the specific phenotype of the plants themselves.

8. Claims 47, 49-51 and 55-57 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter that Applicant regards as the invention. Dependent claims are included in all rejections.

Applicant's arguments filed 15 November, 2001, have been fully considered but they are not persuasive.

Applicant urges that the claims as written are clear and concise and that no confusion exists as to the relationship of the components and that altering the claims as suggested in the last Office action would lead to confusion.

This is not found persuasive.

Claim 47 is indefinite for its recitation of the phrase "isogenic for an expression cassette". "Isogenic" means genetically identical over the entire genome. Thus, "isogenic for an expression cassette" has no meaning.

In claim 47, part (d) is it not clear if the plant from part (b) is crossed to the second plant or to some other plant. If the former is intended, "and" should be replaced with --with--.

Claims 47 and 49 are indefinite in their recitation of the phrase "recombinase minus". It is unclear what is intended by this term - does the progeny lack the recombinase enzyme? The gene? Does it have a mutant version of the recombinase gene?

In claim 50, the phrase “being selected such that an expression product thereof” is so unduly wordy and awkward as to be indefinite. It is suggested that the phrase be replaced with --encoding an expression product that--.

Similarly, in claims 56 and 57, the phrase “are selected such that” should be replaced with --encode polypeptides that cause-- and “is” should be replaced with --to be--.

Claim 57 recites the limitation “said offspring” in line 2. There is insufficient antecedent basis for this limitation in the claim.

Claim 55’s recitation of “Plants seeds each of which comprising a genome” and subsequent references to “genome” is wordy and awkward. A genome is an inherent feature of a plant seed and thus does not need to be recited.

Claim 55 is indefinite for its recitation of the phrase “functionally-hemizygotic”. The phrase is not defined by the specification and has no meaning in the art. “Hemizygotic” means a gene is present on one chromosome and not the other, so it is difficult to imagine what is intended by “functionally-hemizygotic” - maybe Applicant means that the exogenes are identical but one is inactivated?

9. Claim 47 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. Both steps (c) and (d) depend from step (b). As the claim is written, there appears to be no purposes for step (c). It is not clear if there are missing steps between steps (c) and (d) or if step (c) is unnecessary.

Claim Rejections - 35 USC § 102

10. Claim 55 remains rejected under 35 U.S.C. 102(b) as being anticipated by Vergunst et al, as stated in the prior Office action.

Applicant's arguments filed 15 November, 2001, have been fully considered but they are not persuasive.

Applicant urges that the plants generated by Vergunst et al cannot exhibit exogenic allelism as defined by the specification because one of the genes in the plants used by Vergunst is expressed from both chromosomes, and as such functional segregation of this gene will not occur in progeny. Applicant also argues that the resemblance in the constructs of Vergunst et al to the constructs in Figure 1 of the instant specification do not translate into functional similarities. Applicant also argues that incorporation of a recombinase and recombinase sites in the construct can lead to less than optimal segregation of the two exogenes with gametes. As such Applicant has amended the claims to include the term "functionally hemizygotic to indicate that a functional (expressible) copy of exogene now exists one in one chromosome of the pair.

This is not found persuasive. The exogene on one chromosome of the plants described by Vergunst has the *bar* gene, and the exogene on the second chromosome has the *bar* and the *nptII* genes. As "functionally hemizygotic" has no art-recognized meaning, nor is it defined in the specification, the term was given no weight. Additionally, the plants of Vergunst et al are exactly analogous to the plants of Figure 1, which are homozygous for the T7 Polymerase gene and hemizygous for the Toxin gene. As Applicant considers the plants of Figure 1 to exhibit true exogenic allelism, the presence of the *bar* gene on both chromosomes in the plants of Vergunst et al is irrelevant. Note that the definition of "exogenic allelism" in the instant specification is

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the “allelic positioning of two functionally distinct exogenes on the chromosomes of a chromosome pair such that substantially 100% segregation of the two exogenes is observed upon gamete formation” (paragraph spanning pg 26-27), and the definition of exogenes is “polynucleotide sequences which are trans-introduced and integrated in a genome of a species” (pg 27, lines 3-5). Whether or not the gene is expressed is not a component of the definition.

The plants of Vergunst et al showed segregation with a χ^2 test for goodness of fit yielding $P > 0.05$ (pg 2732, right column, paragraph 1). Thus, the conditions of segregation and the definition of exogenic allelism have been met by the plants of Vergunst et al.

11. Claim 55 remains rejected under 35 U.S.C. 102(b) as being anticipated by Fabijanski et al, as stated in the prior Office action.

Applicant’s arguments filed 15 November, 2001, have been fully considered but they are not persuasive.

Applicant urges that Fabijanski et al do not teach or suggest methods of generating true exogenic allelism and the plants they describe would not exhibit obligatory segregation of the two genes to different gametes.

This is not found persuasive. This examiner is not in a position to evaluate the enablement of claims of an issued patent. The method of claim 9 of the issued patent states that it is one that produces seed wherein the first and second recombinant DNA molecules are located on opposite chromatids of homologous chromosomes such that segregation of the two recombinant DNA molecules occurs during meiosis. Thus, the method would generate plants in which the exogenes are “functionally hemizygotic”.

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12. Claims 47, 49-51 and 56-57 are free of the prior art, given the failure of the prior art to teach a method of backcrossing plants produced by a recombination system and given the unpredictability inherent in using these recombination systems, as detailed above.

Conclusion

13. No claim is allowed.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne R. Kubelik, whose telephone number is (703) 308-5059. The examiner can normally be reached Monday through Friday, 8:30 am - 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson, can be reached at (703) 306-3218. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the patent analyst, Kimberly Davis, at (703) 305-3015.

Anne R. Kubelik, Ph.D.
January 25, 2002

A handwritten signature in black ink that reads "Amy Nelson". The signature is written in a cursive, flowing style.

**AMY J. NELSON, PH.D
PRIMARY EXAMINER**